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SUMMARY PAGE

THE PROBLEM

To compare susceptibility to motion sickness and the efficacy of exemplary drugs in the prevention of motion sickness in the SRR and airsickness in aerobatics.

FINDINGS

Individual difference in drug effectiveness was demonstrated to be significant at the .01 level or better and was similar under the two conditions. Susceptibility to motion sickness in the SRR was generally a good predictor of susceptibility in aerobatics in eight subjects, but in the remaining two it was grossly in error. A combination of scopolamine and d-amphetamine was by far the most effective of the drugs tested under both conditions.

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INTRODUCTION

In previous reports (4,6,7) from this laboratory a standardized laboratory test procedure was described which was useful in demonstrating individual differences in susceptibility to canal sickness, a type of motion sickness experienced in a rotating environment. The relative value of exemplary drugs of different categories in reducing susceptibility to canal sickness has also been demonstrated (10, 11) by this procedure.

The basic purpose of the present experiment was to extend these studies by demonstrating whether and to what extent the findings in the Slow Rotation Room (SRR) were transferable to another force environment. This was done by comparing in the same group of subjects their susceptibility to motion sickness and the efficacy of exemplary drugs in the prevention of canal sickness in the SRR and airsickness in aerobatics.

PROCEDURE

Eighteen healthy Navy enlisted men, 18-21 years of age, assigned to the Naval Aerospace Medical Institute, were screened in a single (nonmedicated) trial of the aerobatics described below. To allow for possible habituation with continued exposure and to permit maximum separation of end points under the expected drug benefit, the ten most airsickness susceptible were chosen as study subjects.

Seven exemplary drugs were pulverized and each was placed in identical gelatin capsules, as were three individual glucose placebos (Table I).

Each "drug" was presented once to each subject in each environment according to a double blind, order-confounding, Latin Square schedule (Table II). This design was developed by R. J. Wherry, Jr., (9) for use where learning, adaptation, or residual treatment effects may be suspected to be present. Usable in squares of 4, 6, 10, 12, 16, 18, et cetera units per side, the design provides for a given drug to be both preceded and followed only once by any other drug in the total number of trials. The coding of drugs was changed between the air and SRR trials to avoid repetition of the presentation order.

The rotating force environment was generated in the Pensacola Slow Rotation Room, an essentially circular, windowless room, 15 feet in diameter and centered about the rotational axis of a human centrifuge (4). The Dial Test (6) provided a standardized series of tape-recorder paced head movements in sequences of five motions at six-second intervals. The strength of the canal sickness producing stimulus of gyroscopic forces on the vestibular system with head motion outside the plane of room rotation varies with the speed of rotation. This allows "customizing" the stimulus to subject susceptibility level.

Subject calibration at 7.5, 10, 15, and 20 rpm prior to the SRR portion of the study determined an optimal rotation speed for a given subject so that canal sickness could be expected for the nonmedicated subject in from five to fifteen sequences. When

Table I

Drugs and Dosages Used in Aerobatics and SRR Dial Test Studies

Drug	Dosage (mg)
Scopolamine with d-Amphetamine (Dexedrine)	0.6 10.0
D-Amphetamine (Dexedrine)	10.0
Cinnarazine (Mitronal)	50.0
Cyclizine (Marazine)	50.0
Meclizine (Bonamine)	50.0
Phenoxybenzamine (Dibenzylene)	20.0
Prochlorperazine (Compazine)	10.0
Placebos 1, 2, and 3 (glucose)	----

Table II

Latin Square Used To Schedule the Order of Drug Presentation in the Air or on the SRR *

	Trial									
Subject	1	2	3	4	5	6	7	8	9	10
Hi	1	2	3	4	5	6	7	8	9	10
Le	2	4	6	8	10	1	3	5	7	9
We	3	6	9	1	4	7	10	2	5	8
Br	4	8	1	5	9	2	6	10	3	7
Du	5	10	4	9	3	8	2	7	1	6
Po	6	1	7	2	8	3	9	4	10	5
Ol	7	3	10	6	2	9	5	1	8	4
Se	8	5	2	10	7	4	1	9	6	3
Mi	9	7	5	3	1	10	8	6	4	2
Ho	10	9	8	7	6	5	4	3	2	1

*Numbers inside the square represent drugs.

it was found that no single speed could be used for all ten subjects, 10 and 20 rpm, respectively, were selected as test speeds for each of two groups of five subjects.

The air environment consisted of an observer-monitored subject seated facing aft in the rear compartment of a single-engine A1E "Skyraider" aircraft during a maximum of twenty-four aerobatic maneuvers. After a level climb to 11,000 feet in the working area under VFR conditions, the same pilot throughout performed the following sequence of maneuvers: 1-4) 3.5 G 360° steep turns alternately left and right during which the subject made 45° head tilts forward, back, and to the sides at two-second intervals; 5) nine wing-rocking and porpoising motions with the subject's gaze focused inside the aircraft; 6 and 7) wing-overs left and right; 8 and 9) aileron rolls left and right; 10 and 11) barrel rolls left and right; 12) a split-S with 4 G pullout. During the final six maneuvers, the subject's attention was focused on reading material held in his lap. Maneuvers 1-4 required about 6,000 feet, 5-11 were at a nearly constant altitude, and 12 required 3,000 feet. The entire sequence lasted fifteen minutes and was repeated once after return to 11,000 feet if an end point had not been reached. The same stimulus strength in the air was experienced by all ten subjects.

The end point for diagnosis of motion sickness, based on the criteria shown in Table III was Malaise III (11). When this stage was reached, straight and level flight was immediately resumed or, in the SRR, the head was fixed and rotation stopped. A maximum of twenty-four maneuvers in the air or sixty sequences (300 head movements) on the SRR was allowed if Malaise III was not reached. Subjects were instructed to report the same level of discomfort and a similar end point in each trial. Scoring was in terms of the number of maneuvers (twenty-four maximum) or sequences (sixty maximum) completed in reaching Malaise III.

Data were analyzed in two ways. A rank order of drug effectiveness (the average of the scores of ten subjects for a given drug) and of subject susceptibility (the average of the three placebo scores for a given subject) was obtained for each environment. During the SRR nonmedicated calibration runs, each of the five men later run at 20 rpm in the drug trials was considerably less susceptible than all five men later run at 10 rpm. In assigning a rank order of subject susceptibility, it was assumed that this was also true in the placebo trials. A rank-difference coefficient of correlation for subject susceptibility and drug effectiveness in the two environments was obtained for significance testing.

In addition, since the aerobatic maneuvers were assumed to be comparable, the data were computer analyzed for each environment separately by the analysis of variance. A graphical comparison of drug effectiveness was made, expressing it as the percentage increase in number of maneuvers or sequences for a given drug over that with Placebo 1.

Table III

IMPORTANT VESTIBULAR SYMPTOMS* USED IN DIAGNOSTIC CATEGORIZATION			
PATHOG-NOMONIC	MAJOR	MINOR	DIAGNOSTIC TERMS
VOMIT-ING	RETCHING NAUSEA III OR II INC. SALIV. III OR II PALLOR III COLD SWEAT III DROWSINESS III	 NAUSEA I INC. SALIV. I PALLOR II COLD SWEAT II DROWSINESS II	VESTIBULAR SICKNESS: VOMITING OR TWO MAJOR SYM. OR ONE MAJOR & TWO MINOR MALAISE III:# ONE MAJOR OR TWO MINOR OR ONE MINOR & TWO OTHER MALAISE I: ANY SUBJ. SYM. OR ANY SIGN USUALLY ASSOC. WITH SUBJ. SYM. MALAISE II: ALL OTHER

* IN RARE INSTANCES OTHER SYMPTOMS QUALIFY
# MALAISE III WAS USED AS AN END POINT IN THE PRESENT STUDY

RESULTS

Rank order of subject susceptibility in each environment is shown in Table IV. While those subjects more susceptible to sickness in the air were generally so on the SRR, exceptions occurred, e.g., subjects Le and Po. The rank-difference coefficient of correlation was not significant at the .05 level.

Rank order of drug effectiveness in each environment is shown in Table V. The rank-difference coefficient of correlation for the two conditions was significant at the .05 level.

In the analysis of variance, drug effect was significant at the .01 and .001 levels in the air and SRR, respectively. Subject susceptibility in the air was significant at the .001 level. However, while a given subject was rotated at a constant speed for the drug trials, allowing a rank order of susceptibility to be assigned based on the calibration run data, subject susceptibility on the SRR was not meaningful since different subjects were rotated at two different speeds for the drug trials.

Trial order was not significant in either condition; habituation was not shown under these exposure conditions.

Graphical comparison of drug effectiveness in the air and in the SRR is shown in Figure 1. Those drugs most effective in the air were generally most effective on the SRR. The three separately treated placebos were very closely grouped (as to effectiveness) in both environments, indicating their validity for control purposes.

The scopolamine/d-amphetamine mixture was by far the most effective in both conditions. Compared to Placebo 1, the mixture increased tolerance in the air by 78 per cent and in the SRR by 188 per cent. No drug was more effective than scopolamine with d-amphetamine in seven subjects in the air and in eight in the SRR.

D-amphetamine alone was the second most effective drug in both environments, being the most effective (alone or one of two) for three of the ten subjects in the air and one on the SRR. In the air, cyclizine, cinnarazine, and meclizine provided the best protection for one subject each; on the SRR, cinnarazine was the most effective in two subjects. Dibenzylene had an unfavorable effect in both environments while meclizine apparently led to an increase in susceptibility in the SRR.

Side effects were minor and randomly dispersed with respect to drugs and subjects; scopolamine plus d-amphetamine did not produce symptoms significantly different or greater than placebos.

DISCUSSION

In the present study it was not possible to equate completely one aerobatic maneuver with all others, although they were roughly similar in stress duration, type,

Table IV

Rank Order of Subject Susceptibility in the Air and SRR*

	Subject									
	Ho	Le	Mi	Br	Ol	Se	Po	We	Du	Hi
Air	1.5	1.5	3.0	4.0	5.5	5.5	7.5	7.5	9.0	10.0
SRR	2.0	9.0	3.0	6.0	5.0	4.0	1.0	7.0	8.0	10.0

* 1 = Most sensitive; 10 = least sensitive

Table V

Rank Order of Drug Effectiveness in the Air and SRR*

Drug	Air	SRR
Scopolamine and d-Amphetamine	1	1
d-Amphetamine	2	2
Prochlorperazine (Compazine)	3	7
Cyclizine (Marazine)	4	4
Placebo 2	5	5
Meclizine (Bonamine)	6	10
Placebo 3	7	6
Cinnarazine (Mitronal)	8	3
Placebo 1	9	8
Phenoxybenzamine (Dibenzylene)	10	9

* 1 = Most effective; 10 = least effective

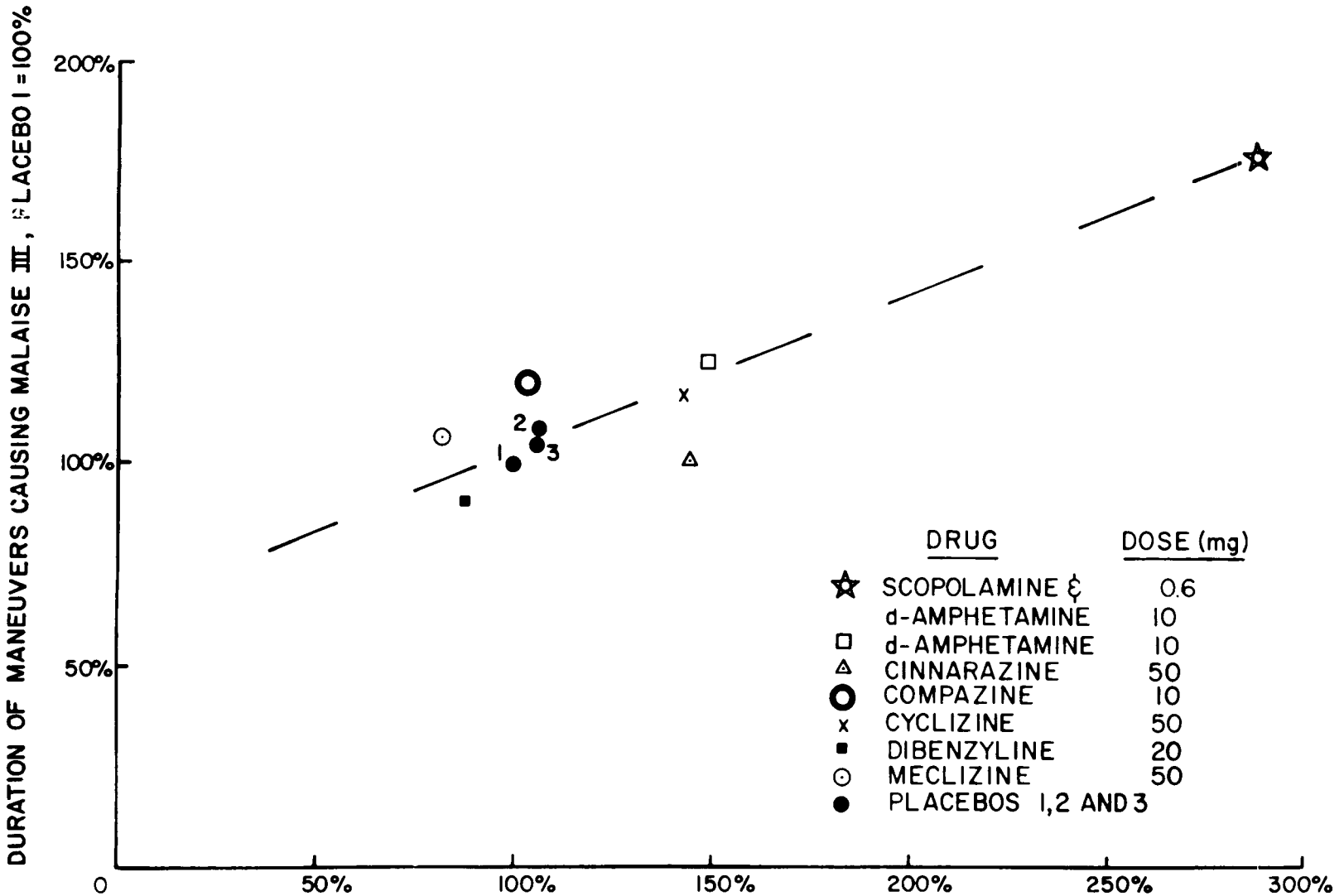

Figure 1

Comparison of Antimotion Sickness Drug Effectiveness in 10 Subjects in the Air and on the SRR Dial Test

and strength. Hence, in the strictest sense, only a rank order comparison of drug effectiveness and of subject susceptibility was possible. Considering rank-difference coefficients of correlation at the .05 level, the SRR Dial Test provided valid information regarding the effectiveness of exemplary drugs under the air conditions of the experiment.

Additional data are provided by assuming that one aerobatic maneuver was essentially equivalent to every other, thereby making the number of maneuvers a linear function of stress provided. With this assumption, drug effectiveness in the air and SRR was significant at the .01 and .001 levels, respectively, and may be compared as in Figure 1. The essentially linear placement of points supports the application of the SRR drug data to aerobatic conditions as does the close grouping of the three placebos treated individually.

The SRR Dial Test with the Malaise III end point has many advantages. It provides a standardized, reproducible stimulus which may be widely varied in strength, ended immediately by head fixation and cessation of rotation, and repeated with a minimum of adaptation or the reduction of subject motivation due to emesis, allowing a subject to serve as his own control. It appears that this laboratory test procedure is more useful than some other devices, e.g., swings, which have been somewhat doubtful indicators of drug effectiveness under field conditions (2). Extension of this test procedure to other drugs with extrapolation to air conditions seems warranted, allowing great savings in experimental outlay while providing field applicable information.

While this study confirms that susceptibility to SRR canal sickness generally predicts sensitivity to airsickness under aerobatic conditions (7), a correlation which is not significant at the .05 level was found. Other studies (2) have shown that susceptibility in one motion sickness producing environment is not an infallible predictor for another. One might speculate that variability in flight experience and anxiety levels, as well as the differences in the stimuli provided in the two environments, may be contributory.

Within the exemplary drugs studied, scopolamine, a parasympatholytic, combined with d-amphetamine, a sympathomimetic, was the most effective medication by a wide margin; d-amphetamine alone was second in both environments, confirming studies in this laboratory (10, 11) and others (1,2,5,8, 12). Dibenzylene, a sympatholytic, was shown to increase motion sickness susceptibility slightly as reported by Chinn et al.(3). These findings harken to earlier theories (5) which noted that motion sickness symptoms resemble parasympathetic overactivity, may be reproduced by anticholinesterases such as physostigmine, and might be prevented or reduced by drugs shifting the balance toward the sympathetic. It is difficult to reconcile a single centrally active mechanism with these facts since scopolamine has a depressant action and both d-amphetamine and Dibenzylene are stimulants. However, Dibenzylene has the reported central side effect of producing nausea and emesis in nonmoving environments.

Compazine, a phenothiazine tranquillizer, was moderately effective in the aerobatic portion (third, next to d-amphetamine), probably through reduction of anxiety. In the SRR it was ineffective as in previous studies (10, 11).

The three antihistamines, cyclizine, cinnarazine, and meclizine, provided contradictory results. Cyclizine was moderately effective in both experimental environments while the related cinnarazine was effective in the SRR but not in the air. Meclizine provided a contrast to previous findings (10-12) in that it was ineffective in the air and increased susceptibility in the SRR. However, subject Hi, usually the most motion sickness resistant subject and high scorer, had an atypical, extremely low score and probably during his SRR meclizine trial, a mild gastroenteritis was developing. Recalculation of rank order of drug effects on the SRR, eliminating Hi's scores, places meclizine in a somewhat effective range (sixth) while changing other positions little. Aside from speculation as to the quality of meclizine stock used, no other explanation can be given.

This study supports the contention that the SRR Dial Test is an effective standardized laboratory procedure for the investigation of antimotion sickness drugs and that findings, generally, may be extrapolated to air conditions. Further antimotion sickness drug screening, the establishment of the optimal scopolamine and d-amphetamine combination, and comparison of drug effectiveness at sea and on other motion simulators are suggested.

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Seven exemplary antimotion sickness drugs and three "individually treated" placebos were investigated in ten men during twenty-four aerobatic maneuvers in an A1E "Skyraider" aircraft and in performance of the Pensacola Slow Rotation Room Dial Test. The rank order of drug effectiveness and of subject susceptibility under each condition was determined and compared.

Individual difference in drug effectiveness was significant at the .01 level or better and was similar under the two conditions. Susceptibility to motion sickness in the SRR was generally a good predictor of susceptibility in aerobatics in eight subjects, but in the remaining two it was grossly in error. A combination of scopolamine and d-amphetamine was by far the most effective of the drugs tested under both conditions.

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